REMARKS

Applicant respectfully submits the below comments in response to the remaining rejections pending in this application, relating to obviousness in view of at least the combination of Tobiasch and Snijder (identified below). Applicant believes that the below remarks will overcome these remaining rejections, and requests Allowance of all "presently pending" and currently unamended claims 1, 4-12, 14-19, 21-25, which include withdrawn claims 21-23, therefore.

The present claims are not obvious under 35 U.S.C. §103(a) over Tobiasch in view of Snijder.

In the present Action, claims 1, 4-8, 10, 15-19, 24 and 25 are rejected under 35 U.S.C. 103(a) as obvious over Tobiasch et al. (Virus Genes 22(2):187-99 (2001)) in view of Snijder (J. Virol. 73(8):6335-6345 (1999)).

Claim 1 is drawn to a vaccine composition protective against equine arteritis virus (EAV) infections in horses. This vaccine is shown to induce a cellular immune response and comprises a nucleic acid encoding an EAV sequence consisting of open reading frame (ORF) 2 which is SEQ ID NO:2, ORF5 which is SEQ ID NO:5 or SEQ ID NO:9 and ORF7 which is SEQ ID NO:7.

I.

As mentioned above, the vaccine of claim 1 includes an EAV sequence consisting of ORF2 + ORF5 + ORF7. The Examiner rejected claim 1, asserting Tobiasch teaches that "EAV is a member of the Arteriviridae family" and that "prevention of EAV in horses by DNA vaccination." Additionally, the Examiner states that "the cDNA sequence of ORF3, ORF4, ORF5 and ORF7 (Table 1) were molecularly cloned into the corresponding sites of expression vectors pCR3.1, pDisplay, and/or pcDNA3.1/HisC" and that the Tobiasch vaccines comprise "one or several vectors, each comprising the aforementioned individual EAV ORF" and points to a mouse vaccination example using a construct expressing ORF5 + ORF7 (in Tobiasch on page 193). See the Office Action, page 3. The Examiner acknowledges that Tobiasch "does not disclose EAV ORF2, together with ORFs 5 and 7 in the same nucleic acid." See the Office Action, page 4, lines 3-4.

Citing Snijder, the secondary reference, the Examiner asserted that Snijder discloses ORF2, in particular the "minor envelope glycoprotein" and would rectify the defect of Tobiasch. As such, the Examiner concluded that that a person of ordinary skill in the art would be motivated to modify the Tobiasch composition so as to combine ORF5 and ORF 7 "with one or more antigens such as ORF2 into an immunogen expressed by the same vector": i) to induce a

broad-range immune response against all arteriviral structural proteins, or to augment the immunogenic effect of ORF5+7 with an additional ORF like ORF2; and ii) to generate immune responses that better mimic the wild type EAV with all structural proteins. See the Office Action, page 4. Applicant respectfully disagrees for at least the following reasons.

I-a.

A 103 rejection was made in the Office Action previously issued in this application, on June 24, 2009 that is similar to the one raised presently. Page 8 lines 7-15 of the present Action (mailed March 19, 2010) states that Applicant's November 20, 2009 submission in response to the June 24, 2009 Action was found unpersuasive because:

> the "30% immune response" quoted by the Applicant is the result when the neutralizing titer 1:20 is excluded, but the amount of immune response including the neutralizing titer 1:20 is actually 70% (page 195, Table 2). Consequently, the difference in the amount of immune response generated by ORF5 or ORF7 alone and by the combination of ORF5+ORF7 is not as substantial as Applicant asserted.

In response, Applicant respectfully submits that the difference in the amount of immune response generated by ORF5 or ORF7 alone and by the combination of ORF5+ORF7 **is as substantial** as Applicant indicated in the November 20, 2009 Amendment.

In particular, Applicant respectfully directs the Examiner to Tobiasch page 195, far right column of Table 2, entitled "% of Immun-Response[b]" [*sic*]. The **"b" superscript**, indicating that the neutralizing titer 1:20 was excluded, applies to **each of the numbers indicated** in that column of Table 2 *unless expressly indicated otherwise* (i.e. with a different superscript). The comparisons made in the November 20, 2009 Amendment properly **compared immune response percentages displayed under superscript "b"** in the far right column of Tobiasch Table 2. In view of the Examiner's comments otherwise made at page 8 and elsewhere in the present Action, Applicant respectfully requests that the Examiner reconsider Tobiasch Table 2 and Applicant's remarks made in the November 20, 2009 Amendment therefore, since the instant application is being presently rejected based on a different interpretation of the Tobiasch Table 2 data. (For convenience, Applicant reproduces part of the past remarks below at Section II).

Because Tobiasch in Table 2 clearly shows that **ORF 5 and ORF 7 together** produced an immune response in only **30%** of the tested mice compared to **truncated EAV ORF5 alone** which produced a **90%** immune response under the same experimental conditions, it is unclear to Applicant why the skilled person, seeking to create a highly immunogenic EAV vaccine for use in horses, would be motivated to begin with, and modify, a disclosure whose teachings as a whole clearly demonstrate a poor immunogenic response of an EAV ORF5+7 combination vaccine in mice (considering the guidance in e.g. MPEP 2141.02). One skilled in the art reading

Figure 2 of Tobiasch would conclude that either the **truncated ORF5** or the **ORF 7/nucleocapsid protein** vaccines having **90%** and **80%** immunogenic response, respectively, are the most desirable and would thus be deterred from seeking an alternative EAV ORF vaccine that includes an ORF combination yielding poor immunological protection under the same experimental conditions. In this connection, to the extent that Tobiasch strongly dissuades a skilled person from seeking a vaccine alternative including ORF5+7, it teaches away a skilled person from adding the ORF2 of Snijder in the manner asserted by the Examiner.

Accordingly, Applicant respectfully notes that the Examiner should not disregard the findings of Tobiasch concerning the inferior protective response of the ORF5+7 combination compared to, for instance truncated ORF5 (or ORF7) alone when evaluating the patentability of the vaccine of claim 1. In view of the above, the Examiner's ground for this rejection seems to be unsustainable.

I-b.

In the present Action, the Examiner further indicates that it would be obvious to the skilled person to modify Tobiasch with Snijder because it would be obvious to add additional structural proteins (i.e. ORF2, Snijder) to make a better vaccine (see e.g. page 8 lines 16-21, page 4 lines 11-19, et al., of the present Action).

However, as indicated in the November 20, 2009 Amendment, and discussed above, Tobiasch Table 2 shows that adding an additional structural protein to ORF5 or ORF7 did not make a better vaccine, but in fact resulted in a substantially reduced immune response compared with ORF5 or ORF 7 alone (as stated: 30% vs. 90% and 80%, respectively, under the same experimental conditions). To emphasize, Tobiasch Table 2 shows that a combined ORF 5 and ORF 7 vaccine resulted in only 30% of animals tested experiencing an immune response, in comparison with 90% tested with the first 121 amino acids of the large envelope protein of ORF 5, 80% tested with an ORF 7/nucleocapsid protein, and 70% or 50% tested with non-truncated ORF 5.

Applicant also notes that the 70% immune response referred to at page 8 lines 7-15 of the present Action is labeled with **superscript "d",** and thus is expressly different from numbers relating to **subscript "b"**. As indicated in the Action, superscript "d" in Tobiasch Table 2 indicates that a neutralizing titer 1:20 was included in the % immune response. The **only entry** that the 70% immune response referred to by the Examiner can be compared to in Table 2 is the **100% entry in the last entry of the table, also indicated with a superscript "d"**. Applicant notes that as Table 2 indicates a **100%** immune response in the Tobiasch vaccine having **ORF5 alone**, and only **70%** in a vaccine consisting of **ORFs 5 + 7**, but in the presence of neutralizing antibodies at a titer of 1:20, this data indeed supports Applicants other assertions regarding Tobiasch in Table 2.

As the Examiner is aware, the teachings of an entire document, including teachings away from a claimed invention, must be considered when rejecting an application under 35 U.S.C. §103. Contrary to instant claim 1, which requires at least ORF5+7 in the claimed vaccine composition, Tobiasch teaches a poor immunogenic response of EAV ORF5+7 compared to either ORF 5 or 7 alone, therefore suggesting that these two ORFs might actually attenuate each other when used together. Tobiasch even underscores this point by stating that the "[h]ighest NT-titers were observed when the animals were administered with the cDNA of ORF 5" (see page 198, left-hand column, last paragraph) which would undoubtedly deter the skilled person from modifying Tobiasch's comparatively weakly immunogenic ORF5+7 combination construct with Snijder's ORF2, at least because of the results shown in Tobiasch Table 2 (page 195), namely that adding an additional structural protein to ORF5 significantly decreased the immunogenic response in the mice tested.

Regarding ORF2, Tobiasch acknowledges that Snijder reported about the "transcriptional activity" of a part of ORF2 that was thought to be untranslated, namely the "novel gene" ORF2a, see Tobiasch page 198, right column, last paragraph), but expressly states that "[b]ased on this knowledge" at least in part, "the construction of a new generation of DNA vaccine against EAV infection must be seriously considered" (*see* Tobiasch, page 199, right-column, 1st full paragraph), which indicates that the specific use of ORF2 in an EAV has not yet been investigated by Snijder, or other researchers; thus ORF2 as an immunoprotective vaccine is not known nor can be assumed. Moreover, the skilled person would immediately realize that the Snijder disclosure is an identification and characterization paper of ORF 2 rather than a paper investigating the particular role of ORF2 as a vaccine in an animal model. At best, Snijder indicates that the expression of EAV ORFs 2a, 5 and/or 6 "in vaccinia virus-based expression systems did not result in the production of subviral particles (data not shown)". See Snijder on page 6344, right-hand column, 1st paragraph. Because Snijder is devoid of any kind of guidance or direction demonstrating that an ORF2 composition alone specifically elicits a protective immunity against an EAV infection (using for instance a reasonable animal model system), and does not provide even one example of how an EAV ORF2 vaccine is made, the skilled person could not readily anticipate, without impermissible hindsight, that the ORF2 of Snijder could be used to modify, and/or correct the deficiencies of the Tobiasch vaccines to thereby arrive at a vaccine having the specific sequence and same immunoprotective properties as the vaccine composition of claim 1.

Consequently, the complete omission of any specific information regarding the immunoprotection of EAV ORF2 coupled with the teaching that a ORF 5+7 vaccine combination is inferior to either ORF 5 or 7 alone should be construed as a clear indicia of the nonobviousness of the present invention.

For the reasons set forth above, and in view of those arguments already of record, Applicant considers that prima facie obviousness has not been established, that independent claim 1 is non-obvious over Tobiasch in view of Snijder. Applicant thus respectfully requests that this rejection be reconsidered and withdrawn.

II.

Reiteration of certain arguments submitted November 20, 2009:

Because the interpretation of Tobiasch, Table 2 is being used to support the present 103 rejection, Applicant respectfully reiterates (briefly) several pertinent observations submitted in response to the previous Action, for the Examiner's convenience, as additional support that the present invention is not obvious in view of Tobiasch and Snijder therefore.

Specifically, Applicant respectfully directs the Examiner to entries in Tobiasch, Table 2 (page 195), that disclose results of vaccination using ORF expression vectors in mice:

- The 8th (last) entry, disclosing vaccination with a construct including the first 121 amino acids of the **large envelope glycoprotein of ORF5**, provided the *highest* immune response - **90%** of animals tested showed an immune response when compared with control.
- The 2nd entry (vaccine: **ORF 7/nucleocapsid protein**) shows that **80%** of animals tested experienced an immune response.
- The 3rd and 4th entries (vaccine: **non-truncated ORF 5**) show that **70%** and **50%** of animals experienced an immune response, respectively.
- The 5th entry (vaccine: ***combined ORF 5 and ORF 7 expression vector***), shows that **30%** of animals experienced an immune response.

Considering the above experimental results, one skilled in the art considering Tobiasch Table 2 would most certainly understand that **the best result** (immune response in 90% of animals) was achieved via administration of **truncated EAV ORF5 alone**, the second best result (immune response in 80% of animals) was found with a construct having ORF 7 alone, and the third-best results were achieved with non-truncated ORF 5 alone (immune response in 70-50% of animals). Significantly, the skilled person would immediately realize that administration of **ORF 5 and ORF 7 together** produced an immune response in only **30%** of the tested animals – a diminishment (e.g. attenuation) in immune response by up to 2/3 following the administration of either ORF 5 or ORF 7 alone.

Taken as a whole, while Tobiasch does disclose a vector construct including ORF 5+7, said vector clearly leads away from the ORF 2+5+7 construct of the present invention. Where one ORF (5 alone or 7 alone) significantly induced immune response, but two ORFs (5+7) greatly reduced immune response, the use of a third ORF (2+5+7) could not be reasonably foreseen by the skilled person to enhance the EAV immune response, whether considering Tobiasch alone or in view of Snijder. By showing that ORF 5 alone produced a significant immune response, and ORF 7 alone produced a significant immune response, but that together ORF 5+7 reduced the incidence of immune response by up to 2/3, Tobiasch must be

fairly construed to teach away from combining ORF 2 with the ORF 5+7 construct. At least for the foregoing reasons, Applicant requests that the Examiner withdraw the present rejection.

Furthermore, in response to the Examiner's concern that ORF 2, 5 and 7 are obvious to combine in a vaccine merely because they are on the **same reading frame** (Tobiasch Fig. 1), Applicant respectfully emphasizes that Tobiasch teaches the skilled person that the inclusion of a combination of ORF 5 and ORF 7 (both on the same reading frame) in a single vector significantly attenuated immune response in mice. One skilled in the art, presented with this knowledge that the combined ORF 5+7 construct substantially decreases the immune response in mice, would not be taught that combining ORFs from the same reading frame would offer enhanced immune protection as a matter of course as the Examiner asserts, but rather, the skilled person reading Table 2 of Tobiasch would immediately understand that combining ORF 5 with ORF 7 would be undesirable, since this combination is not useful in inducing an immune response to EAV.

In addition to the above, Applicant respectfully notes that the present invention was devised by two authors of the Tobiasch document – M. Giese and G. Darai. These gentlemen recognized the need for a vaccine for EAV, and engaged in research to consider EAV components that may be useful in preparing an effective EAV vaccine for horses. Early research did include the mouse model described by Tobiasch, and data shown therein. Only after performing additional research, did the two inventors discover that the present invention, namely the specific combination of ORF 2+5+7, provided for a highly effective EAV vaccine in horses, and filed the present patent application. It is Applicant's hope that the above discussion clarifies that the present invention was not actually taught in any way by Tobiasch, but rather is the result of further research and inventive endeavor.

III.

For a complete record, turning to the additional rejections under 35 USC 103 in view of Tobiasch, Snijder in combination with either Cantlon, Krieg or Gregoriadis in the present Action on pages 5-7, Applicant respectfully submits that these rejections should be considered as overcome at least for the same reasons as those set forth above and in view of the argumentation already of record.

CONCLUSION

In view of the discussion set forth above, in particular regarding the findings depicted in Tobiasch at Table 2, Applicant believes that the rejections to the present application in the Office Action mailed on March 19, 2010 have been overcome, and that the pending claims are in good condition for grant. Accordingly, Applicant requests that the Examiner rejoin the withdrawn claims and issue a notification of allowance.

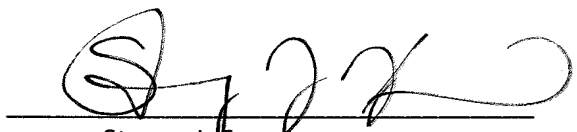
In the event that the Examiner maintains any rejections in this application, Applicant respectfully requests that the Examiner issue a new Office Action detailing such rejections, as page 8 of the present Action indicates that remarks submitted in Applicant's November 20, 2009 Amendment were not fully considered. Also, Applicant kindly requests that the Examiner point out specific technical passages of the cited documents that support the Examiner's case against the patentability of the present invention, so that the Applicant may more closely consider the Examiner's concerns.

If the Examiner believes that a telephone call would expedite the allowance of the present case, the Examiner is respectfully requested to contact Applicant's undersigned attorney at the number indicated below, or the additionally authorized representative, Mrs. Neymeyer-Tynkov, whose contact information can be found in correspondence submitted to the U.S. PTO today, May 19, 2010.

No fees are believed to be due in connection with this correspondence. Communication using email has been authorized by Applicant's attorney.

Respectfully submitted,

Dated: May 19, 2010



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